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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/775,648	02/05/2001	Toshiaki Takezawa	202785US0X	3290

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 10/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/775,648	TAKEZAWA ET AL.	
	Examiner	Art Unit	
	Maria B Marvich, PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-56* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2001* is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 8/5/04. Claims 1-36 have been cancelled. Claims 37-56 have been added. Claims 37-56 are pending in this application.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. The new grounds of rejection herein were necessitated by amendment and, therefore, this action is final.

Claim Objections

Claim 37 is objected to for reciting "at least one mesh networks". The term "networks" should be singular. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection necessitated by applicants' amendment.**

Claim 37 is vague and indefinite in that the metes and bounds of the word "cell incorporated type three-dimensionally reconstructed tissue can become a scaffold" are unclear.

By use of "can become", it is unclear if the "cell incorporated type three-dimensionally reconstructed tissue" must be a scaffold or simply has the potential to become a scaffold.

Claim 37 is vague and indefinite in that the metes and bounds of the term "derived from" are unclear. It is unclear the nature and number of steps required to obtained a "derivative" of ovum. The term implies a number of different steps that may or may not result in a change in the functional characteristics of the ovum from the source that it is "derived from". It would be remedial to amend the claim language to use the term "obtained from", which implies a more direct method of acquiring tissue.

Claim 37 is vague and indefinite in that the metes and bounds of "further comprises at least one cell, at least one extracellular matrix (ecm) and at least one mesh networks" are unclear. The structural and functional relationship of the additional cells, ecm and mesh to the "cell incorporated type three-dimensionally reconstructed tissue" is constructed is unclear. It is unclear if these are components added to the reconstructed tissue or separate from it.

Claims 38, 39, 43 and 47-56 recite the limitation "the cells incorporated in the co-culturing carrier" in claim 37. There is insufficient antecedent basis for this limitation in the claim. Claim 37 teaches that "a cell incorporated three-dimensionally reconstructed tissue" is used for co-culturing the fertilized ovum of an animal but does not that recite cells that are incorporated or an actual step of culturing which would provide an antecedent basis for the recited cells that are incorporated.

Claims 47-56 are vague and indefinite in that the metes and bounds of the term "with feeding a culture medium to the fertilized ovum and the cells incorporated in the co-culturing carrier" are unclear. It is unclear what is being fed, the animal, the ovum or the ovum and cells.

As recited, however, the claims recite that the culture medium is fed. Furthermore, it is not clear what is intended by "culture medium to the fertilized ovum". Does this statement mean that the culture medium is specific to the fertilized ovum or that the culture medium is simply added to the media?

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37-39, 43-49 and 53-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spaulding et al (US patent 6,001,643; see entire document) in view of Schinstine et al (US 5,840,576; see entire document). **This rejection is maintained for reasons of record in the office action mailed 5/5/04 and is applied to new claims 37-56.**

Applicants claim a co-culturing carrier for co-culturing a fertilized ovum of an animal comprising a cell-incorporated type three-dimensionally reconstructed tissue for the purpose of adhesion and three-dimensional growth, which can become a scaffold for growing three-dimensional tissue from the fertilized ovum, is tissue/organ engineered and further comprises at least one cell, ecm and mesh network. The carrier further comprises Collagen I and/or a mesh network and is pretreated with mitomycin C.

Spaulding et al teach use of a hydrodynamic cell culture environment comprised of a tissue culture chamber for three-dimensional tissue growth (column 9, line 44-57). As a general

method, material is introduced into a roller bottle that is suitable for cell and tissue culture i.e. polystyrene, nylon and the like (column 7, line 20-30). Cells are suspended in media in the chamber and as the cells aggregate, they form an autologous extracellular matrix upon which cells adhere, differentiate and become 3-dimensional tissue (column 14, line 61–column 15, line 1). Specifically for use in developing embryos, Spaulding et al teach co-culturing of a fertilized ovum of an animal with endometrial tissue in the chamber. Therefore, the carrier of Spaulding et al comprises a scaffold (endometrial tissue) for the cellular growth of a fertilized egg once it is implanted. Spaulding teaches that the endometrial tissue (which is comprised of epithelial cells and stromal cells) is co-cultured with the fertilized egg such that endometrial implantation constructs are formed that support endometrial maturation until it is transplanted into a recipient uterus (example 8, column 20, line 29-56). Cellular growth is accomplished in culture medium (see e.g. col 8, line 53-55).

Spaulding et al do not teach use of mitomycin pretreated cells or an extracellular matrix such as collagen I or a mesh network as part of the co-culturing carrier.

Schinstine et al teach use of mitomycin C to control cell growth of dividing cells so that a supply of differentiated cells is generated (see e.g. column 7, line 44-52 and column 13, line 23-31). Furthermore, extracellular matrix proteins alone or in combination with a physical matrix or other growth controlling substance (see e.g. column 14, line 33-39) are used to decrease proliferation and increase differentiation (see e.g. column 15, line 11-22). The extracellular matrix is gelled and includes collagen I (see e.g. example 4, page 24).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate into the co-culturing carrier taught by Spaulding et al the extracellular

matrix or mitomycin C taught by Schinstine et al because Spaulding et al teach that it is within the ordinary skill of the art to develop a scaffold comprised of differentiating endometrial cells for the co-culturing of a fertilized ovum and because Schinstine et al teach that it is within the ordinary skill of the art to culture cells for tissue engineering in the presence of mitomycin C or with extracellular matrix. One would have been motivated to do so in order to receive the expected benefit of decreased proliferation and increased differentiation which is desired in the generation of engineered tissue (see Schinstine et al, column 15, line 11-22). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claim 40-42 and 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spaulding et al (US patent 6,001,643; see entire document) in view of Schinstine et al (US 5,840,576; see entire document) further in view of Goff and Smith (Theriogenology, 1998, 49:1021-1030; see entire document). **This rejection is maintained for reasons of record in the office action mailed 5/5/04 and is applied to new claims 37-56.**

Applicants claim a co-culturing carrier for co-culturing a fertilized ovum of an animal comprising a cell-incorporated type three-dimensionally reconstructed tissue comprised of bovine endometrial epithelial or stromal cells.

The teachings of Spaulding et al and Schinstine et al are described above and are applied as before except;

Spaulding et al and Schinstine et al do not teach use of bovine endometrial epithelial or stromal cells.

Goff and Smith teach use of Bovine endometrial cells for Co-culture after IVF (see abstract). The Bovine endometrial cells were able to maintain the embryo development to blastocyte stage (see e.g. page 1027, paragraph 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate into the co-culturing carrier taught by Spaulding et al and Schinstine et al the bovine endometrial cells taught by Goff and Smith because Spaulding et al and Schinstine et al teach that it is within the ordinary skill of the art to develop a carrier for the co-culturing of a fertilized ovum comprised of endometrial cells and because Goff and Smith teach that it is within the ordinary skill of the art to co-culture an embryo with Bovine endometrial cells. One would have been motivated to do so in order to receive the expected benefit that bovine cells are readily available for purchase, can survive at least 10 doublings and maintain embryo development to the blastocyte stage (see Call Application on line catalog and Goff and Smith page 1027, paragraph 1). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 103(a) on pages 10-13 of the amendment filed 8/5/04. Applicants argue that the art does not disclose or suggest a carrier for development of tissue with three-dimensional architecture having an early embryo-like structure

such that a gastrula or a neurula is protected but at most suggest carriers for development to blastocyst or to just before formation of gastrula. Rather, applicants argue, "no reports currently exist of a culture carrier or a co-culturing carrier on which a fertilized ovum of an animal is cultured to induce three-dimensional growth" (page 9, line 10-12). Applicants point toward several deficiencies of Spaulding et al such that it fails to anticipate or render obvious the instant invention. 1) In the instant method, the cells are suspended in one or more gelated ecm and mixed with mesh networks to produce cell sheets that inhibit contraction of the cell incorporated three-dimensionally reconstructed tissue. Spaulding et al generate construct like cell-sheets on a wall by rotation of a bottle filled with cells. 2) The instant carrier facilitates culturing while maintaining an implantation-like state. To perform this function, the cell gel sheet containing mesh networks like gauze is removed from a culture vessel and floated in a culture medium. The epithelial cells come into contact with the fertilized ovum and a layer of stromal and epithelial cells form gland-like structures within the gel "at a distance from epithelial cells". These results were unexpected. 3) The epithelial-like cells form a three-dimensional tubular gland like structure that is nothing like the simple uterine gland-like structure of Spaulding.

Applicants' arguments filed 8/5/04 have been fully considered but they are not persuasive. The co-culturing carrier and methods of using the carrier is not distinguishable from the invention of Spaulding et al in view of Schinstine et al or Goff and Smith for the following reasons. The instant invention recites a carrier for co-culturing a fertilized ovum comprising a cell incorporated type three-dimensionally reconstructed tissue for the purpose of adhesion and three-dimensional growth that can become a scaffold for growth, is obtained from cells, tissues or organs and further comprises at least one cell, one ecm and mesh network. Spaulding et al

teach a carrier for co-culturing a fertilized ovum (see e.g. col 9, line 44-57). The carrier is generated by introduction of cells and a mesh network into a roller bottle. The cells initially grow and aggregate and generate an autologous ecm "upon which cells adhere, differentiate and become three-dimensional tissue" (see e.g. col 14, line 65 through col 15, line 1). While Spaulding teaches rotation of a vessel to generate the three-dimensional cell and tissue growth, this is not excluded by the instant claims. The "tissue engineering" generates three-dimensionally reconstructed tissue that can be designed for multiple purposes depending on the cell type (see e.g. col 16, line 46-48). In the case of growth of fertilized eggs, endometrial tissue is co-cultured with the egg. The endometrial tissue forms endometrial implantation constructs that support embryonic maturation. The endometrial implants eventually form decidua with phenotypic and morphological attributes that characterize implantation (col 20, line 45-56). Therefore, reconstructed tissue is generated that is a scaffold for the fertilized egg to grow.

Therefore, Spaulding et al specifically teach a culture system for growing three-dimensional tissues or organs that can be used for culturing a fertilized ovum to three-dimensional growth. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Applicants have pointed out three distinctions between the carrier of Spaulding and the instant invention. As indicated above, these distinctions relate to the method in which the carrier of the instant invention has been constructed and to specific

structural characteristics of the carrier. However, neither the method of producing the carrier nor the structural characteristics are recited embodiments and therefore carry no patentable weight. During prosecution claims must be interpreted as broadly as the terms reasonably allow, limitations from the specification are not read into the claims.

Applicants argue that unexpected results were obtained in that the epithelial cells come into contact with the fertilized ovum and a layer of stromal and epithelial cells form gland-like structures within the gel at a distance from epithelial cells once the cell gel sheet containing mesh networks like gauze is removed from a culture vessel and floated in a culture medium to co-culture with fertilized ovum. Applicants, however, have provided no evidence of the unexpected results nor demonstrated the occurrence of the unexpected results. Rather, applicants have simply provided objective opinion that the stromal and epithelial cells form a gland like structure. Furthermore, applicants have not indicated what characteristic of the instant invention is responsible for the unexpected results. As the instant invention and the carrier of Spalding et al in view of Schinstine et al appear to comprise the same components for the same end, it is not clear that the invention of Spalding et al would not generate those same unexpected results and as such in view of Schinstine et al and Goff and Smith render the instant invention obvious.

Conclusion

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1636

April 22, 2004

GERRY LEFFERS
PRIMARY EXAMINER